Amendments to the Specification:

Please replace the paragraph beginning on page 1 at line 5 with the following amended paragraph:

This invention relates to the use of the IL-2 ~~common~~ receptor gamma chain, also known as the common gamma chain (cγc), and related molecules for the modulation of signal activities controlled by NIK, and some new such molecules.

Please replace the paragraph beginning on page 4 at line 11 with the following amended paragraph:

Like other MAP3Ks, NIK can be activated as a consequence of phosphorylation of the 'activation loop' within the NIK molecule. Indeed, mutation of a phosphorylation-site within this loop (Thr-559) prevents activation of NF-κB upon NIK overexpression [Lin et al. 1999]. In addition, the activity of NIK seems to be regulated through the ability of the regions upstream and downstream of its kinase motif to bind to each other. The C-terminal region of NIK downstream of its kinase moiety has been shown to be capable of binding directly to IKKα [Regnier et al. 1997] as well as to p100 [Xiao et al. 2001] and to TRAF2 [Malinin et al. 1997]. ~~these~~ These interactions are apparently required for NIK function in NF-κB signaling. The N-terminal region of NIK contains a negative-regulatory domain (NRD), which is composed of a basic

motif (BR) and a proline-rich repeat motif (PRR) [Xiao et al. 2000]. Apparently, the N-terminal NRD interacts with the C-terminal region of NIK in cis, thereby inhibiting the binding of NIK to its substrate (IKKα and p100). Ectopically expressed NIK seems to spontaneously form oligomers in which these bindings of the N-terminal to the C-terminal regions in each NIK molecule are apparently disrupted, and display a high level of constitutive activity [Lin et al. 1999]. The binding of the NIK C-terminal region to TRAF2 (as well as to other TRAF's) most likely participates in the activation process of NIK. However, its exact mode of participation is unknown.

Please replace the paragraph beginning on page 5 at line 1 with the following amended paragraph:

There is likewise rather limited information yet of the downstream mechanisms in NIK action. Evidence has been presented that NIK, through the binding of its C-terminal region to IKKα can activate the IκB kinase (IKK) complex. It has indeed been shown to be capable of phosphorylating serine-176 in the activation loop of IKKα, ~~and its activation~~ thereby activating IKKα [Ling et al. 1998]. ~~Consistently~~ Consistent with such mode of action, studies of the mechanisms accounting ~~to~~ for the deficient activation of NF-κB by the LTβR in *aly/aly* mice murine embryonic fibroblasts (MEF's) indicated

that NIK mutation ablates activation of the IKK signalosome and the consequent phosphorylation of IκB [Matsushima et al 2001]. These findings were not supported, however, by the analysis of MEF's derived from NIK -/- mice. Although the NIK deficient MEF's are unable to manifest NF-κB activation in response to LTβ, they do seem to respond normally to it in terms of IκB phosphorylation and degradation [Yin et al. 2001]. According to these findings, NIK may not participate at all in the activation of the IKK complex by the LTβR but is rather involved by an as yet unknown mechanism in controlling the transcriptional action of the NF-κB complex after its translocation to the nucleus. There are also still uncertainties as to the way by which NIK triggers p100 phosphorylation and processing. Its ability to bind p100 directly through its C-terminal region and phosphorylate it suggests that p100 serves as a direct NIK substrate [Xiao et al. 2000]. Nevertheless, a recent study has suggested that NIK mediates p100 phosphorylation in an indirect way, through phosphorylation and thus activation of IKKα that in turn phosphorylates p100 [Senftleben et al.2001].

Please replace the paragraph beginning on page 9 at line 6 with the following amended paragraph:

Murine and human gamma subunits of the receptor have approximately 70 percent sequence identity at the nucleotide and amino acid levels. This subunit is required for the generation of high and intermediate affinity IL2 receptors but does not bind IL2 by itself. These two receptor types consist of an alpha-beta-gamma heterotrimer and a beta-gamma heterodimer, respectively. The gene encoding the gamma subunit of the IL2 receptor maps to human chromosome Xq13, spans approximately 4.2 kb and contains eight exons. Relationships to markers in linkage studies suggest that this gene and SCIDX1, the gene for X-linked severe combined immunodeficiency, have the same location. Moreover, in each of 3 unrelated patients with X-linked SCID, a different mutation in the IL2R-gamma gene has been observed.

Please replace the paragraph beginning on page 10 at line 1 with the following amended paragraph:

The present invention relates to the use of IL-2 ~~common~~ receptor gamma chain (also known as common gamma chain (cγc)) or a mutein, variant, fusion protein, preferably 41MDD (SEQ ID NO:2), 44MPD(SEQ ID NO:17), the intracellular domain of cγc (ICDcγc) (SEQ ID NO:1), 1-357 (SEQ ID NO:20) 1-341(SEQ ID NO:21, functional derivative, circularly permutated

derivative or fragment thereof for modulating the interaction between cγc and NIK

Please replace the paragraph beginning on page 10 at line 8 with the following amended paragraph:

In addition the ~~ivention~~ invention relates to the use of a DNA encoding cγc or a mutein, variant, fusion protein, circularly permutated derivative or fragment thereof, a DNA encoding the antisense of cγc, an antibody specific to cγc, or a small molecule obtainable by screening products of combinatory chemistry in a luciferase system, for modulating the interaction between ~~IL-2~~ common gamma chain (cγc) and NIK.

Please replace the paragraph beginning on page 10 at line 26 with the following amended paragraph:

Moreover, the present invention relates to a pharmaceutical composition comprising cγc or a mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment thereof, the specific DNA, antisense DNA, antibody or small molecule obtainable by screening products of combinatory chemistry in a luciferase system for modulating the interaction between ~~IL-2~~ common gamma chain (cγc) and NIK or in diseases wherein NIK or NF-κB activity is involved in the pathogenesis of the disease.

Please replace the paragraph beginning on page 11 at line 9 with the following amended paragraph:

The invention provides a DNA ~~ancoding~~ encoding cγc of the invention, a vector harbouring the DNA, and a host cell comprising the vector.

Please replace the paragraph beginning on page 11 at line 14 with the following amended paragraph:

The invention also provides a polypeptide fragment of cγc, comprising the NIK binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment thereof, preferably ~~preferably~~ 41MDD (SEQ ID NO:2), 44MPD(SEQ ID NO:17), the intracellular domain of cγc (ICDcγc) (SEQ ID NO:1), 1-357 (SEQ ID NO:20) and 1-341(SEQ ID NO:21.

Please replace the paragraph beginning on page 12 at line 9 with the following amended paragraph:

In addition, the invention relates to the use of a fragment of cγc~~,~~ comprising the NIK binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment thereof, in the manufacture of a medicament for the treatment and/or

prevention of autoimmune diseases such as immune thyroiditis, rheumatoid arthritis and other ~~arthropatics~~arthropathies, autoimmune haemolytic anemia and inflammatory bowel disease.

Please replace the paragraph beginning on page 12 at line 14 with the following amended paragraph:

In another embodiment the invention relates to a method for the treatment and/or prevention of a disease in which activation of NF-κB is involved in the pathogenesis of the disease, or in a disease ~~a disease~~ in which NIK and cγc interaction is involved in the pathogenesis of said disease, comprising administering a therapeutically effective amount of cγc, or a mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment thereof to a subject in need.

Please replace the paragraph beginning on page 12 at line 20 with the following amended paragraph:

In a further embodiment the ~~invetion~~ invention provides a method of treatment and/or prevention of a disease in which NF-κB activation is involved in the pathology of the disease such as cancer , rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis, comprising

administering to a host in need thereof an effective amount of a small molecule according to the invention, or comprising administering a therapeutically effective amount of cγc, or a mutein, variant, fusion protein, functional derivative, circularly permutated derivative or fragment thereof to a subject in need

Please replace the paragraph beginning on page 14 at line 11 with the following amended paragraph:

Figure 4 shows the concentration-dependent effect of cγc on NIK induced NF-κB activation. Activation of NF-κB is monitored by the luciferase reporter assay (for details see Example 10). NF-κB activation in 293-T cells was induced by overexpressing NIK. Luciferase expression was monitored in cells transfected with the following plasmids: empty plasmid (sample pc), empty plasmid and a plasmid encoding luciferase under the control of an NF-κB inducible promoter (pcDNA3luciferase, 0.5 µg/well) (sample pc+luc), 1 µg pcS3MTNIK and pcDNA3luciferase (sample NIK 1mcg), 1 µg pcS3MTNIK, 0.1 µg/well pcDNA3cγc and pcDNA3luciferase (sample NIK+~~cgc~~ cγc 0.1mcg), 1 µg pcS3MTNIK, 0.5 µg/well pcDNA3cγc and pcDNA3luciferase (sample NIK+~~cgc~~ cγc 0.5 mcg), and 1 µg pcS3MTNIK with 1 µg/well pcDNA3cγc and pcDNA3luciferase (sample NIK+~~cgc~~ cγc 1 mcg).

Please replace the paragraph beginning on page 14 at line 22 with the following amended paragraph:

Figure 5 shows the effect of a dominant negative mutant of NIK (dnNIK, residues 624-947) on cγc enhanced NF-κB activation. Activation of NF-κB is monitored by the luciferase reporter assay (for details see Example 10). NF-κB activation in 293-T cells was induced by overexpressing NIK. Luciferase expression was monitored in cells transfected with the following plasmids: empty plasmid (sample pc), empty plasmid and a plasmid encoding luciferase under the control of an NF-κB inducible promoter (pcDNA3luciferase) (sample pc+luc), pcS3MTNIK and pcDNA3luciferase (sample NIK), pcS3MTNIK, pcS3MTdnNIK and pcDNA3luciferase (sample NIK+dnNIK) pcDNA3cγc and pcDNA3luciferase (sample ~~egc~~cγc), pcS3MTNIK, pcDNA3cγc and pcDNA3luciferase (sample NIK+~~egc~~cγc), pcS3MTdnNIK, pcDNA3cγc and pcDNA3luciferase (sample ~~egc~~cγc+dnNIK), pcS3MTNIK, pcDNA3cγc, pcS3MTdnNIK and pcDNA3luciferase (sample NIK+~~egc~~cγc+dnNIK). pcS3MTdnNIK, pcS3MTNIK and pcDNA3cγc were used at a concentration of 1, 1, and 0.1µg/well respectively.

Please replace the paragraph beginning on page 15 at line 7 with the following amended paragraph:

Figure 6 shows the effect of cγc on NF-κB activation induced by the NIKaly mutant. Activation of NF-κB is monitored by the luciferase reporter assay (for details see Example 10). NF-κB activation in cells is induced by overexpressing NIK. Luciferase expression was monitored in 293-T cells transfected with the following plasmids: empty plasmid (sample pc), empty plasmid and a plasmid encoding luciferase under the control of an NF-κB inducible promoter (pcDNA3luciferase) (sample pc+luc), pcS3MTNIK and pcDNA3luciferase (sample NIK), pcDNA3luciferase and pcDNA3cγc (sample ~~egc~~cγc), pcS3MTNIK, pcDNA3cγc and pcDNA3luciferase (sample NIK+~~egc~~cγc), 1 µg pcS3MTalyNIK and pcDNA3luciferase (sample alyNIK) and pcS3MTalyNIK, pcDNA3cγc and pcDNA3luciferase (sample alyNIK+~~egc~~cγc). pcS3MTalyNIK, pcS3MTNIK and pcDNA3cγc were used at a concentration of 1, 1, and 0.1µg/well respectively.

Please replace the paragraph beginning on page 15 at line 19 with the following amended paragraph:

Figure 7 shows the effect of a 41 amino acid polypeptide derived from the membrane distal end of cγc (41MDD) on NIK induced NF-κB activation and enhancement by full-length cγc. Activation of NF-κB is monitored by the luciferase reporter assay (for details see Example 10). NF-κB

activation in 293-T cells was induced by overexpressing NIK. Enhancement of NF-κB induction is obtained by overexpressing NIK and expressing the full cγc at low concentration. Luciferase expression was monitored in cells transfected with the following plasmids: empty plasmid (sample pc), empty plasmid and a plasmid encoding luciferase under the control of an NF-κB inducible promoter (pcDNA3luciferase) (sample pc+luc), pcS3MTNIK and pcDNA3luciferase (sample NIK), pcS3MTNIK, pcDNA3cγc and pcDNA3luciferase (sample NIK+~~egc~~cγc), pcS3MTNIK, a plasmid expressing GST (pGST) and pcDNA3luciferase (sample NIK+GST), pcS3MTNIK, pcDNA3cγc, pcGST and pcDNA3luciferase (sample NIK+GST+~~egc~~cγc), pcS3MTNIK, pcDNA3cγc, pcGST-41MDD and pcDNA3luciferase (sample NIK+~~egc~~cγc+41GST). The plasmids pcS3MTNIK, pcDNA3cγc, pcGST-41MDD and pcDNA3luciferase were used at concentrations of 0.5, 0.05, 2 and 0.5 µg/ml respectively.

Please replace the paragraph beginning on page 16 at line 6 with the following amended paragraph:

Figure 8 shows the effect of cγc deletion mutants, deleted at the C-terminal end of the protein, and on NIK induced NF-κB activation. Activation of NF-κB is monitored by the luciferase reporter assay (for details see Example 10).

NF-κB activation in Hela cells was induced by overexpressing NIK. Luciferase expression was monitored in cells transfected with the following plasmids: empty plasmid and a plasmid encoding luciferase under the control of an NF-κB inducible promoter (pcDNA3luciferase) (sample pc+luc), pcS3MTNIK and pcDNA3luciferase (sample NIK), pcS3MTNIK, pcDNA3cγc and pcDNA3luciferase (sample NIK +~~cgc~~cγc), pcS3MTNIK, pcDNA3cγc357 and pcDNA3luciferase (sample NIK+1-357), pcS3MTNIK, pcDNA3cγc341 and pcDNA3luciferase (sample NIK+1-341), pcS3MTNIK, pcDNA3cγc325 and pcDNA3luciferase (sample NIK+1-325) and pcS3MTNIK, pcDNA3cγc303 and pcDNA3luciferase (sample NIK+1-303). Plasmids pcS3MTNIK, pcDNA3cγc/deleted, pcDNA3luciferase, were all used at the same concentration of 0.5μg/ml. Total amount of DNA used was normalized with empty plasmid pcDNA3.

Please replace the paragraph beginning on page 17 at line 1 with the following amended paragraph:

Figure 10 shows the effect of overexpression of full ICD cγc or its 41 amino acid membrane distal domain on NF-κB activation induced via the LTβ receptor. Activation of NF-κB is monitored by the luciferase reporter assay (for details see Example 10). NF-κB activation in mouse embryonic fibroblast cells was induced with LTβ. Luciferase expression was

monitored in cells transfected with the following plasmids: empty plasmid (sample pc), a plasmid expressing GST (pcGST) and pcDNA3luciferase (sample pcGST+luc), a plasmid encoding the GST fusion protein with the intracellular domain of cγc (pGSTICcγc) and pcDNA3luciferase (sample GSTIC~~cgc~~cγc+luc) and a plasmid encoding the GST fusion with the 41 polypeptide from the membrane distal domain of cγc (pGST41MDD) and pcDNA3luciferase (sample GST-41MDD+luc). Plasmids pGSTICcγc, pGST41MDD, and were used at 1 µg/well and pcDNA3luciferase were used at a concentration of 0.5 µg/well. Empty plasmid, pcDNA3 was used as a carrier to normalize the total DNA concentration to 2µg/well. The levels of luciferase activity are expressed in relative light units (RLU).

Please replace the paragraph beginning on page 18 at line 17 with the following amended paragraph:

The invention relates to the modulation of ~~IL-2~~ common gamma chain (cγc) and NIK interaction in pathologies involving said interaction.

Please replace the paragraph beginning on page 22 at line 8 with the following amended paragraph:

As mentioned above, interaction of endogenous NIK and cγc was demonstrated in peripheral mononuclear blood

cells. It was found that in mononuclear cells NIK is constitutively associated with cγc, and upon IL-2 induction the signalosome components IKK-1, IKK-2, and IKK-3 are recruited to the IL-2 receptor ~~trough~~ through cγc. The ~~IL-2 receptor~~ common γ chain was found to bind to NIK at a different location, other than the IKK-1 binding region. Similar results were obtained upon stimulation of the cells with IL-15.

Please replace the paragraph beginning on page 22 at line 14 with the following amended paragraph:

The signalosome components co-immunoprecipitated with cγc upon IL-2 stimulation ~~was~~ were shown to be active in a kinase assay. Thus these results demonstrate that under physiological conditions, binding of endogenous cγc to NIK occurs, and that this interaction is involved in NIK activity and in NIK dependent NF-κB activation. Therefore, inhibiting the interaction of cγc and NIK may bring ~~to~~ about inhibition of NF-κB activation.

Please replace the paragraph beginning on page 23 at line 27 with the following amended paragraph:

The term "circularly ~~permuted~~permutated" as used herein refers to a linear molecule in which the termini have

been joined together, either directly or through a linker, to produce a circular molecule, and then the circular molecule is opened at another location to produce a new linear molecule with termini different from the termini in the original molecule. Circular permutations include those molecules whose structure is equivalent to a molecule that has been circularized and then opened. Thus, a circularly ~~permuted~~ permutated molecule may be synthesized de novo as a linear molecule and never go through a circularization and opening step. The particular circular permutation of a molecule is designated by brackets containing the amino acid residues between which the peptide bond is eliminated. Circularly ~~permuted~~ permutated molecules, which may include DNA, RNA and protein, are single-chain molecules, which have their normal termini fused, often with a linker, and contain new termini at another position. See Goldenberg, et al. J. Mol. Biol., 165: 407-413 (1983) and Pan et al. Gene 125: 111-114 (1993), both incorporated by reference herein. Circular permutation is functionally equivalent to taking a straight-chain molecule, fusing the ends to form a circular molecule, and then cutting the circular molecule at a different location to form a new straight chain molecule with different termini. Circular permutation thus has the effect of essentially preserving the

sequence and identity of the amino acids of a protein while generating new termini at different locations.

Please replace TABLE A on page 26 with the following amended TABLE A:

TABLE A Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
Ser	Ser, Thr, Gly, Asn
Arg	Arg, Gln, Lys, Glu, His
Leu	Ile, Phe, Tyr, Met, Val, Leu
Pro	Gly, Ala, Thr, Pro
Thr	Pro, ~~Ser.~~Ser, Ala, Gly, His, Gln, Thr
Ala	Gly, Thr, Pro, Ala
Val	Met, Tyr, Phe, Ile, Leu, Val
Gly	Ala, Thr, Pro, ~~Ser.~~Ser, Gly
Ile	Met, Tyr, Phe, Val, Leu, Ile
Phe	Trp, Met, Tyr, Ile, Val, Leu, Phe
Tyr	Trp, Met, Phe, Ile, Val, Leu, Tyr
Cys	Ser, Thr, Cys
His	Glu, Lys, Gln, Thr, Arg, His
Gln	Glu, Lys, Asn, His, Thr, Arg, Gln
Asn	Gln, Asp, Ser, Asn
Lys	Glu, Gln, His, Arg, Lys
Asp	Glu, Asn, Asp
Glu	Asp, Lys, Asn, Gln, His, Arg, Glu
Met	Phe, Ile, Val, Leu, Met
Trp	Trp

Please replace TABLE B on page 28 with the following amended TABLE B:

TABLE B More Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
~~Sers~~Ser	~~Sers~~ Ser
~~Arc~~Arg	His, Lys, Arg
Leu	Ile, Phe, Met, Leu
Pro	Ala, Pro
Thr	Thr
Ala	Pro, Ala
Val	Met, Ile, Val
Gly	Gly
~~Ilea~~Ile	Ile, Met, Phe, Val, Leu
Phe	Met, Tyr, Ile, Leu, Phe
~~Try~~Tyr	~~Phi~~Phe, Tyr
Cys	Ser, Cys
His	Arg, Gln, His
Gln	Glu, His, Gln
Asn	Asp, Asn
Lys	Arg, Lys
Asp	Asn, Asp
Glu	~~FLN~~Gln, Glu
Met	Phe, Ile, Val, Leu, Met
Trp	Trp

Please replace TABLE C on page 29 with the following amended TABLE C:

TABLE C Most Preferred Groups of Synonymous Amino Acids

Amino Acid	Synonymous Group
~~Sers~~Ser	~~Sers~~ Ser
~~Arc~~Arg	~~Arc~~Arg
Leu	Ile, Met, Leu
Pro	Pro
Thr	~~Thar~~Thr
~~Alan~~Ala	~~Alan~~Ala
Val	Val
Gly	Gly
~~Ilea~~Ile	Ile, Met, Leu
~~Phi~~Phe	~~Phi~~Phe
~~Try~~Tyr	Tyr
Cys	Ser, Cys
His	His
Gln	Gln
Asn	Asn
Lys	Lys
Asp	Asp
Glu	Glu
Met	Ile, Leu, Met

Trp Trp

Please replace the paragraph beginning on page 30 at line 5 with the following amended paragraph:

Muteins in accordance with the present invention include those encoded by a nucleic acid, such as DNA or RNA, which hybridizes to DNA or RNA under stringent conditions and which encodes said protein in accordance with the present invention, comprising essentially all of the naturally-occurring sequences encoding for example cγc and fragments of cγc comprising regions responsible for binding NIK such as 41MDD and 44MPD, 1-357 and 1-341. For example, such a hybridising DNA or RNA ~~maybe~~ may be one encoding the same protein of the invention having, for example, the sequences set forth in Figs. 13 and 14 (SEQ ID~~: N5~~ NO:5 and 6 encoding ICDcγc and 41MDD, respectively), and sequences which may differ in its nucleotide sequence from the naturally-derived nucleotide sequence by virtue of the degeneracy of the genetic code, i.e., a somewhat different nucleic acid sequence may still code for the same amino acid sequence, due to this degeneracy.

Please replace the paragraph beginning on page 30 at line 16 with the following two amended paragraphs:

The term "hybridization" as used herein shall include any process by which a strand of nucleic acid joins with its complementary strand through a base pairing (Coombs J, 1994, Dictionary of Biotechnology, ~~stokton~~ Stockton Press, New York NY).

"Amplification" is defined as the production of additional copies of a nucleic acid sequence and is generally carried out using polymerase chain reaction technologies well known in the art (Dieffenbach and Dveksler, 1995, PCR Primer, a Laboratory Manual, Cold Spring Harbor Press, Plainview NY).

Please replace the paragraph beginning on page 31 at line 8 with the following amended paragraph:

where M is the molarity of monovalent cations, %GC is the percentage of G and C nucleotides in the DNA, % form is the percentage of formamide in the hybridization solution, and L is the length of the hybrid in base pairs. For each ~~1 C~~1°C that the Tm is reduced from that calculated for a 100% identity hybrid, the amount of mismatch permitted is increased by about 1%. Thus, if the Tm used for any given hybridization experiment at the specified salt and formamide concentrations is ~~10 C~~ 10°C below the Tm calculated for a 100% hybrid according to the equation of Meinkoth, hybridization will occur even if there is up to about 10% mismatch.

Please replace the paragraph beginning on page 31 at line 16 with the following amended paragraph:

As used herein, "highly stringent conditions" are those which provide a Tm which is not more than ~~10 C~~ 10°C below the Tm that would exist for a perfect duplex with the target sequence, either as calculated by the above formula or as actually measured. "Moderately stringent conditions" are those~~, which~~ that provide a Tm, which is not more than ~~20 C~~ 20°C below the Tm that would exist for a perfect duplex with the target sequence, either as calculated by the above formula or as actually measured. Without limitation, examples of highly stringent (5-~~10 C~~ 10°C below the calculated or measured Tm of the hybrid) and moderately stringent (15-~~20 C~~ 20°C below the calculated or measured Tm of the hybrid) conditions use a wash solution of 2 X SSC (standard saline citrate) and 0.5% SDS (sodium dodecyl sulfate) at the appropriate temperature below the calculated Tm of the hybrid. The ultimate stringency of the conditions is primarily due to the washing conditions, particularly if the hybridization conditions used are those~~, which~~ that allow less stable hybrids to form along with stable hybrids. The wash conditions at higher stringency then remove the less stable hybrids. A common hybridization condition that can be used with the highly stringent to

moderately stringent wash conditions described above is hybridization in a solution of 6 X SSC (or 6 X SSPE (standard saline-phosphate-EDTA), 5 X Denhardt's reagent, 0.5% SDS, 100 ~~µ~~ µg/ml denatured, fragmented salmon sperm DNA at a temperature approximately 20 to ~~25 C~~ 25°C below the Tm. If mixed probes are used, it is preferable to use tetramethyl ammonium chloride (TMAC) instead of SSC (Ausubel, 1987, 1999).

Please replace the paragraph beginning on page 33 at line 11 with the following amended paragraph:

The present invention provides cγc and fragments of cγc comprising regions responsible for binding NIK such as 41MDD and 44MPD, 1-357 and 1-341, peptides derived therefrom, or a mutein, fusion protein, functional derivative, circularly permutated derivative or fragment thereof, or salt thereof for the manufacture of a medicament for the treatment of inflammatory diseases.

Please replace the paragraph beginning on page 34 at line 13 with the following amended paragraph:

Thus, conjugating peptides, proteins or oligonucleotides to molecules that are known to bind to cell surface receptors will enhance membrane permeability of said peptides, proteins or oligonucleotides. Examples ~~for~~ of

suitable groups for forming conjugates are sugars, vitamins, hormones, cytokines, transferrin, asialoglycoprotein, and the like molecules. Low et al., USP 5,108,921, describes the use of these molecules for the purpose of enhancing membrane permeability of peptides, proteins and oligonucleotides, and the preparation of said conjugates.

Please replace the paragraph beginning on page 39 at line 11 with the following two amended paragraphs:

The anti-Id Mabs thus have their own idiotypic epitopes, or "idiotopes" structurally similar to the epitope being evaluated.

The term "monoclonal antibody" is also meant to include both intact molecules as well as fragments thereof, such as, for example, Fab and ~~F (ab') 2,~~F(ab')$_2$, which are capable of binding antigen. Fab and ~~F (ab') 2~~F(ab')$_2$ fragments lack the Fc fragment of intact antibody, clear more rapidly from the circulation, and may have less non-specific tissue binding than an intact antibody (Wahl et al., *J. Nucl. Med.* 24:316-325 (1983)).

Please replace the paragraph beginning on page 40 at line 1 with the following amended paragraph:

The definition of "pharmaceutically acceptable" is meant to encompass any carrier~~, which~~ that does not interfere with effectiveness of the biological activity of the active ingredient and that is not toxic to the host to which it is administered. For example, for parenteral administration, the active protein(s) may be formulated in a unit dosage form for injection in vehicles such as saline, dextrose solution, serum albumin and Ringer's solution.

Please replace the paragraph beginning on page 40 at line 21 with the following amended paragraph:

The invention relates to a method for the treatment of a disease involving signalling of a cytokine ~~trough~~ through ~~IL-2~~ cγc in the pathogenesis of said disease comprising administration of a therapeutically effective amount of specific antibodies able to recognise and bind cγc protein and/or to fragments of cγc comprising regions responsible for binding NIK such as 41MDD and 44MPD, 1-357 and 1-341, to a subject in need.

Please replace the paragraph beginning on page 42 at line 3 with the following amended paragraph:

In addition, screening for molecules generated by combinatorial chemistry~~, which~~ that inhibit NIK and IL-2

receptor γ chain ~~receptor~~ interaction comprising a polypeptide comprising the intracellular domain of the cγc or a mutein, fusion protein, functional derivative, active fraction, circularly permutated derivative or fragment thereof, comprising: coating or capturing (by a specific antibody bound to the plate) one of the proteins (e.g. NIK or NIK640-720) in a plate and detecting the binding of the other protein (e.g. cγc, ICDcγc or fragments thereof) bound to the plate with specific antibody in the presence or absence of organic compounds.

Please replace the paragraph beginning on page 43 at line 13 with the following amended paragraph:

More than 5000 clones appeared on the selection plates. About half of the resistant clones were analyzed by α-gal assay and approximately 60% of them turned out positive with varying intensity of blue colour. Plasmids were isolated and purified from 800 colonies. The DNA inserts of 400 plasmids out of the 800 (chosen according to colour intensity which is indicative of affinity of binding) were amplified~~,~~ by polymerase chain reaction (PCR) using primers corresponding to the flanking sequences of the inserts in the cDNA library, and sequenced. Most of the preys detected~~,~~ turned out to be non-specific, e.g.: 80% of the DNA inserts corresponded to 3' and

5' untranslated regions of various genes and 10% to DNA inserts encoding immunoglobulins. The remaining 10% corresponded to segments encoding regions of proteins. Some of the positive colonies turned blue 4-8 days after ~~seeded~~seeding, some after about 8-12 days, and others became coloured late, up to 12-16 days after seeding. The speed of the colour development in positive colonies is indicative of the strength of protein-protein interaction, i.e. the faster the colour appears, the stronger the interaction.

Please replace the paragraph beginning on page 43 at line 26 with the following amended paragraph:

One of the binding proteins found, the IL-2 receptor gamma chain ~~receptor~~, was chosen for further analysis. The IL-2 receptor gamma chain ~~receptor~~ is a subunit of the IL-2, IL-4, IL-7, IL-9, IL-13, IL-15 and IL-21 receptor complexes~~,~~; therefore, it is commonly dubbed as the 'common γ chain' (cγc).

Please replace the paragraph beginning on page 46 at line 5 with the following amended paragraph:

The deletion mutants were created by sequentially ~~introduction~~ introducing ~~of~~ stop codons in the cytoplasmic domain of cγc, in gaps of 10-20 amino acids. The DNA encoding the full-length cγc or its deletion mutants were introduced

into the pGADT7 prey vector (Clontech) for testing their binding to NIK in the SFY526 heterologous yeast strain by the two hybrid assay. The SFY526 yeast strain is prototrophic for TRP and Leu. pGBKT plasmids (bait vector) have the Trp1 wild type gene and pGAD has the wild type Leu2 gene. Thus, only doubly transfected yeast will grow on selective Leu Trp media. Functional GAL4 will be restored in doubly transfected yeast when the chimeric proteins fused to GAL4 domains interact, bringing the activation domain and DNA binding domain of GAL4 to close proximity. The level of LAC-Z expression is indicative of the strength of the protein-protein interaction. Lac-Z activity was assessed by the standard beta-gal/colony lift filter assay (Clontech, Yeast Protocol Handbook, Chapter VI).

Please replace the paragraph beginning on page 46 at line 17 with the following amended paragraph:

Since introduction of cγc and mutants into the pGADT7 prey vector for assessing their binding to NIK as bait manifested high non-specificity, the interactions were tested in the reverse orientation: i.e. deletion mutants were cloned into the bait vector and NIK or C-terminus of NIK (residues 624-947) in the ~~pray~~ prey vector. The results summarized in Table 1 show that none of the deletions, ~~but~~ except the

cytoplasmic domain of cγc (ICD) alone, showed strong binding, to both NIK and NIK C-terminus. The binding of most of the ICD (lacking 5 amino acid from its proximal membrane domain) to both NIK and C-terminus NIK was stronger than that of the full-length cγc molecule. A 50% reduction in affinity to NIK was observed by deleting 12 amino acids or 44 amino acids at the membrane distal end of cγcICD.

Please replace Table 1 beginning on page 47 at line 27 with the following amended Table 1:

Table 1.

cγc amino acid residues	NIK624-947 (C-terminal domain)	NIK	Lamin
Full length (1-369)	+/-	-	-
1-357	-	-	*
1-325	-	-	*
1-303	-	-	*
1-282	-	-	*
289-369 (most of ICD)	++++	+++	-
289-357 (12 aa deleted from the membrane distal domain)	++	*	*
289-325 (44 aa deleted from the ICD)	++	*	*

* Not tested

Please replace the paragraph beginning on page 48 at line 3 with the following amended paragraph:

The binding of 41 MDD polypeptide to full length NIK or C-terminus NIK was tested in both orientations (i.e. 41 MDD as the ~~pray~~ prey and NIK as the bait and vice versa). The

results obtained are shown in Table 2. The interaction is relatively weak when NIK serves as the prey partner, but strong when NIK serves as the bait. The interaction of the 41 MDD is stronger with the C-terminus of NIK than with the full length NIK. These results confirmed that the 41 MDD polypeptide is involved in binding to NIK.

Please replace the heading prior to the paragraph beginning on page 55 at line 12 with the following amended heading:

Effect of cγc in modulating signal transduced ~~trough~~ through the LTβ receptor:

Please replace the paragraph beginning on page 55 at line 12 with the following amended paragraph:

Induction of the LTβ receptor by its ligand, results in NF-κB activation. It is suggested in the literature that NIK participates in signaling ~~trough~~ through the LTβ receptor. Thus, the effect of overexpressing the whole cytoplasmic cγc polypeptide or the 41 distal domain (329-369) on NF-κB activation mediated by the LTβ receptor was tested. Activation of NF-κB was monitored by the luciferase reporter assay (for details see Example 10).

Please replace the paragraph beginning on page 55 at line 18 with the following amended paragraph:

A cell line was prepared from mouse embryonic fibroblast cells, which are generally known to express the LTβ receptor. 10^5 cells of the above line were seeded per well in 6 well plates. 24 hours later transfection was performed (with Gene porter transfection reagent, Gene therapy systems) with the plasmid pcGST ~~ICcgc~~ ICDcγc expressing the intracellular domain of cγc (cγc ~~IDC~~ICD) fused to GST or with pcGST41MDD expressing the 41 distal domain of cγc fused to GST and the expression plasmid encoding luciferase reporter protein under the control of an NF-κB inducible promoter (pcDNA3 luciferase). NF-κB activation was measured indirectly by measuring the luciferase activity present in the cells.

Please replace the paragraph beginning on page 57 at line 6 with the following amended paragraph:

Total DNA concentration was normalized to 2 µg/well with empty vector (pcDNA3). pcGST ~~ICcgc~~ ICDcγc and pcGST41MDD were used at a concentration of about 1 µg/well. 24 hours after the transfection, cells were stimulated with 50ng/ml recombinant LTβ (cat# L-5162, Sigma) for 1 hour.

Please replace the paragraph beginning on page 56 at line 6 with the following amended paragraph:

The above results suggest that cγc may be involved in signaling ~~trough~~ through the LTβ receptor. The cγc 41 distal domain inhibits signaling ~~trough~~ through LTβ receptor, indicating that this polypeptide or fragments thereof may serve as candidates for peptide based drug designing. Such drugs may modulate NIK action and therefore are valuable in preventing or alleviating inflammatory responses or in modulatory immunoregulatory processes.

Please replace the paragraph beginning on page 58 at line 1 with the following amended paragraph:

The two-Hybrid system used for screening was the ~~Matchmaker~~ MATCHMAKER version III (Clontech). In this system the bait gene (NIK gene) is expressed as a fusion to the GAL4 DNA binding domain (DNA-BD), while the ~~pray~~ prey genes or cDNA library is expressed as a fusion to the GAL4 activation domain (AD). When the DNA-BD and AD are brought into proximity, transcription of four reporter genes is activated (encoding HIS, ADE, lacZ and α-gal).

Please replace the paragraph beginning on page 58 at line 9 with the following amended paragraph:

Clones ~~growing~~ are grown on plates under high stringency conditions, i.e. in plates without LEU (selection marker for the bait encoding plasmid), TRP (selection marker for the ~~pray~~ prey encoding plasmid), HIS and ADE and impregnated with substrates for detection of α-gal expression. Plasmids were purified from positive clones by lysis of the yeast cells (with detergent and mechanical stress) followed by phenol extraction and ethanol precipitation of the DNA. cDNA inserts in the plasmids were amplified by PCR with flanking primers specific for the library vector pACT2. Individual amplified cDNAs were directly cloned into a mammalian expression vector for further biochemical analysis.

Please replace the paragraph beginning on page 61 at line 2 with the following amended paragraph:

NIK and cγc interaction was demonstrated in a mammalian cell environment, in lysates of 293-T cells ~~overexpresing~~ overexpressing these proteins (see Example 4). The following experiment was carried with endogenous proteins, in cells naturally expressing these proteins. Thus, peripheral blood mononuclear cells (PMBC) ($500x10^6$ cells) were incubated with IL-2, lysed and immunoprecipitated with anti cγc antibodies (for immunoprecipitation see Example 9). Co-immunoprecipitated proteins bound to cγc were detected in

Western blots using relevant antibodies. The candidate proteins tested for co-immunoprecipitation with cγc were those proteins normally present in the signalosome, such as NIK, IKKα (IKK-1), IKKβ (IKK2), IKKγ (NEMO). The co-immunoprecipitated proteins were tested in lysates of cells tested at time-0 and after four-hour incubation with IL-2. The results summarized in Figure 16 A show that NIK is coprecipitated with cγc before and after stimulation with IL-2. Therefore NIK was found constitutively associated with cγc. Traces of IKK-1 was found in the basal level and upon 4 hours incubation with IL-2, other signalosome components, i.e. IKK-2 and NEMO, were recruited to the IL-2 receptor ~~trough~~ through the cγc. The results indicate that the IL-2 receptor ~~common~~ gamma chain is bound to NIK at a different location than the IKK-1 binding region. Similar results were obtained upon stimulation of the cells with IL-15 (figure 16A right panel).